Articles

Total Synthesis of Archaeal 36-Membered Macrocyclic Diether Lipid

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Total synthesis of archaeal 36-membered macrocyclic diether lipid **2** is reported. The synthesis is based upon stereoselective preparation of functionalized isoprenoid chains, ether-linkage formation between the isoprenoid chains with a glycerol derivative, and the ultimate intramolecular dicarbonyl coupling using low-valent titanium known as McMurry coupling. This synthetic method has successfully provided the first practical route to chemically defined archaeal macrocyclic membrane lipids, which were not available because of the lack of synthetic access. Also described is a highly stereoselective and convenient synthesis of stereochemically homogeneous archaeal biphytanyl glycerol lipid **1**.

Introduction

The archaea (or archaebacteria) including thermophiles, halophiles, acidophiles, alkalophiles, and methanogens are a heterogeneous group of prokaryotes.[1] Most of these microorganisms grow under extreme environments such as high temperature and high acidic and salt-rich conditions and differ markedly from other prokaryotes in their 16S ribosomal RNA sequences and in other important characteristics of cellular composition.[1,2] Archaeal cell membrane lipids are composed of branched isoprenoid-chain hydrocarbons linked to a glycerol molecule at the *sn*-2- and -3-positions by ether linkage. Fatty acid components found in eubacterial and eucaryal lipids are completely absent. The isoprenoid hydrocarbon chains of lipid molecules are frequently joined intramolecularly at the terminal position to form a macrocyclic ring as large as 36- or 72-membered as shown in Figure 1.[2] We have been interested in the chemical and biochemical features of these archaeal lipids. Recently, we have postulated the pathway and stereochemistry of the lipid biosynthesis in the halophiles and the thermoacidophiles.[3] Another area of our interest in these lipids focuses on the biochemical significance of the macrocyclic molecular structures.[4] Several modeling and synthetic studies of these macrocyclic lipids have been reported in terms of their thermostability,[5] since these membrane lipids may provide a clue to the development of a heat-resistant lipid membrane. However, no reports have appeared on the synthesis of natural macrocyclic ring possessing branched isoprenoid chains until our preliminary report on the synthesis of archaeal macrocyclic 36-membered lipids.[4b] In this paper, we report full details of our synthesis of an archaeal macrocyclic membrane lipid featuring the 36-membered ring, which was first isolated from extreme thermophiles *Methanococcus jannaschii*.[2k,l]

Results and Discussion

The basic synthetic plan for **2** was composed of stereoselective preparation of appropriate isoprenoid chains,

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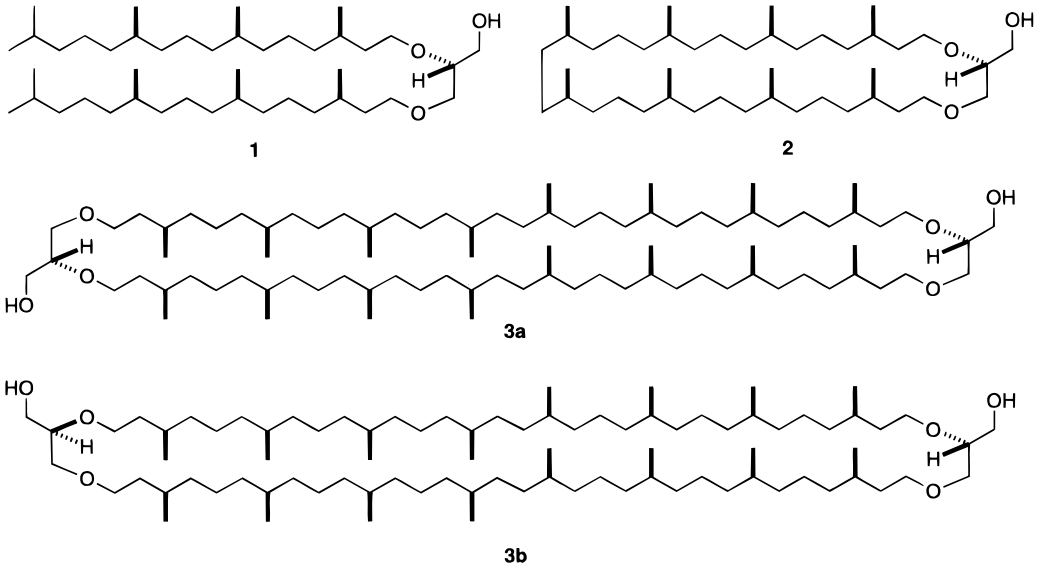

Figure 1. Typical structures of archaeal membrane lipids **1**, **2**, and **3a**,**b**.

subsequent ether-linkage formation with a glycerol derivative, and a crucial intramolecular dicarbonyl coupling using low-valent titanium known as McMurry coupling.[6] Thus, our primary synthetic target was the C_{20} unit **24**.[7] The synthesis of the C_{20} unit **24** was accomplished by coupling relevant two C_{10} units, and the essential building block possessing 10-carbons **12** was prepared in two methods using either methyl (*R*)-3-hydroxy-2-methylpropionate (**4**) or (*R*)-citronellol benzyl ether (**16**) as a chiral starting material.

The first choice of a chiral starting material was commercially available methyl (*R*)-3-hydroxy-2-methylpropionate (**4**). Transformation of **4** into a carbon-5 block **5** was carried out by manipulations similar to those previously reported by Mori *et al*.[8] Thus, a series of reactions comprising from protection of the hydroxyl group of **4** with an ethoxy ethyl group (EE), reduction of the ester group with lithium aluminum hydride, tosylation of the resulting alcohol, and displacement of the tosyloxy group with cyanide ion gave nitrile **5** in 98% overall yield from **4**. Exchange of the protecting group from EE to *tert*-butyldimethylsilyl (TBDMS), followed by repeated reduction with DIBAH, afforded the C_5 unit **7** in 73% yield.

The C_5 unit **7** was treated with I_2-Ph_3P-imidazole in benzene to give in 85% yield iodide **8** as one coupling precursor. The other coupling partner **10** was also derived from **7**. Treatment of **7** with benzyl 2,2,2-trichloroacetimidate in the presence of acid catalyst[9] gave a benzyl ether,[10] which was then hydrolyzed by acid to afford alcohol **9** in 88% yield. At this stage, the enantiomeric purity was determined to be 99% ee as judged from the ^{1}H NMR spectra of (*R*)-α-methoxy-α-(trifluoromethyl)-α-phenylacetate (MTPA) derivative of **9**.[11] Mesylation of **9** followed by displacement of the mesylate with a phenylthio group and oxidation with *m*-CPBA afforded the sulfone **10** in 89% yield. The next step was the coupling between two C_5 units into a C_{10} unit. The reaction between the anion derived from **10** with butyllithium and iodide **8** in THF-HMPA at −25 °C smoothly provided coupling product **11** in 73% yield, which was subesequently treated with Na(Hg) in methanol to afford the bifunctional C_{10} unit **12** in 85% yield. Then, portions of **12** were subjected to either deprotection of the benzyl group or TBDMS group to obtain **13a** and **14a** in 96% and 79% yield, respectively (Scheme 1).

For the alternative synthesis of the precursory bifunctional C_{10} unit, we developed a more efficient and preparative method. The synthesis started from readily available (*R*)-citronellol (**15**) (98% ee) and is summarized in Scheme 2.[12] The readily available (*R*)-citronellol benzyl ether **16**[14] was oxidatively decomposed by ozonolysis, followed by reductive workup of the resulting ozonide with sodium borohydride to furnish alcohol **17** in 93% yield. The tosylate of alcohol **17**, obtained by treatment with tosyl chloride, was treated with an acetylide anion derived from propargyl alcohol tetrahy-

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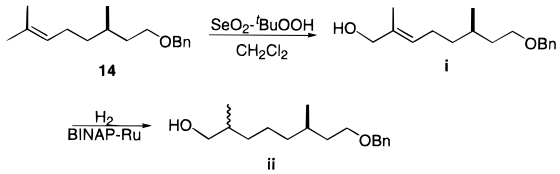
(9) Iversen, T.; Bundle, K. R. *J. Chem. Soc., Chem. Commun.* **1981**, 1240.

(10) Benzylation under basic conditions such as NaH−benzyl halide in DMF or DMSO was not straightforward as migration of the TBDMS group was observed in ca. 30−40% yield.

(11) Dale, J. A.; Dull, D. L.; Mosher, H. S. *J. Org. Chem.* **1969**, *34*, 2543.

(12) Our first attempt to synthesize a C_{10} unit from (*R*)-citronellol involved the asymmetric hydrogenation of readily available (*E*)-allylic alcohol **i** using Noyori's BINAP−Ru-based catalysts.[13] The hydrogenation reactions proceeded smoothly using several BINAP−Ru-based catalysts; however, the diastereomeric purities of the product **ii** were less than 75% in our hands.



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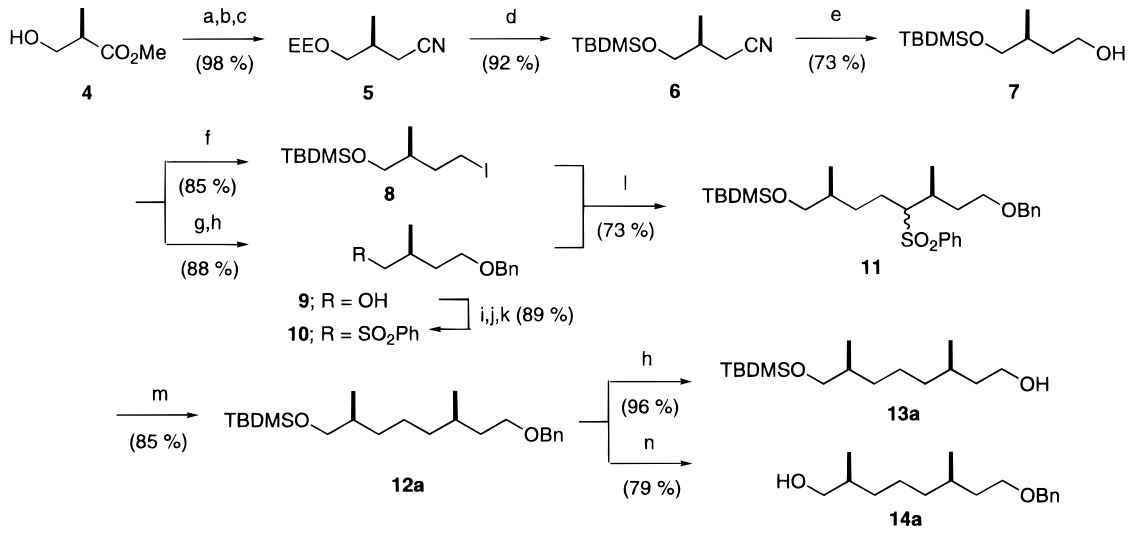
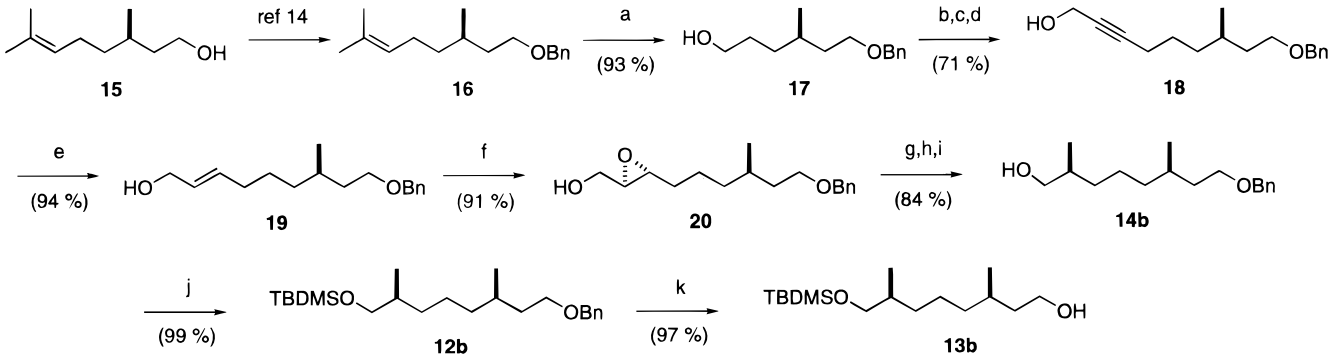
Scheme 1[a]



[a] Reagents: (a) (1) ethyl vinyl ether, PPTS/THF, (2) $LiAlH_4$; (b) TsCl/Py; (c) NaCN/DMSO; (d) (1) 2 N HCl/THF, (2) TBDMSCl, imidazole/DMF; (e) (1) DIBAH/toluene, (2) H_2O, (3) DIBAH/toluene; (f) I_2, Ph_3P, imidazole/benzene; (g) $BnOC(=NH)CCl_3$, TfOH/ether; (h) 2 N HCl/THF; (i) MsCl/pyridine; (j) PhSH, K_2CO_3/DMF; (k) *m*-CPBA/CH_2Cl_2; (l) (1) ^{n}BuLi/THF−HMPA, (2) compound **8**; (m) 5% Na(Hg)/MeOH; (n) H_2, Pd−C/EtOAc.

Scheme 2[a]



[a] Reagents: (a) (1) O_3/MeOH, (2) $NaBH_4$; (b) TsCl/pyridine; (c) $NaC{\equiv}CCH_2OTHP$/DMSO; (d) 2 N HCl/THF−MeOH; (e) $LiAlH_4$/THF; (f) $Ti(O^iPr)_4$, D-(−)-DET, ^{t}BuOOH, molecular sieves 4A/CH_2Cl_2; (g) Me_3Al/CH_2Cl_2; (h) $NaIO_4$/THF−H_2O; (i) $NaBH_4$/MeOH; (j) TBDMSCl, imidazole/DMF; (k) H_2, Pd−C/EtOAc.

dropyranyl ether and hydrolyzed with acid to provide alkynyl alcohol **18** in 71% yield. Reduction of the alkynyl alcohol to allylic alcohol **19** was efficiently accomplished with high selectivity using lithium aluminum hydride in THF at 0 °C. Raising the reaction temperature to 10 °C or above led to generation of an allenic product in 10−20% yield, which was essentially useless for further transformation. The allylic alcohol **19** was subjected to Sharpless asymmetric epoxidation[15] to give epoxide **20** in high yield. Stereoselective epoxide opening with trimethylaluminum in CH_2Cl_2[16] followed by a series of reactions with sodium periodate and with sodium borohydride afforded the C_{10} unit **14b** in 84% yield. The newly formed chiral center of **14b** had 95% diastereomeric purity as judged from ^{1}H NMR spectra of its (*R*)-MTPA ester derivative.[11] The other C_{10} unit **13b** was easily obtained from **14b** in excellent yield.

As shown in Scheme 3, the essential building block **13ab** for the synthesis of a C_{20} unit **23** was converted to iodide **21** in 88% yield by treatment with I_2−Ph_3P−imidazole in benzene. The other building block **14b** was also transformed into sulfone **22** in 85% yield as described for the synthesis of **10**. In the same fashion as in the synthesis of **11**,[7] the iodide **21** and the sulfone **22** were coupled in 87% yield to obtain the intermediary C_{20} unit **23**, which was subsequently treated with lithium in ethylamine−THF to afford the desired C_{20} unit **24** in 59% yield.

Having the C_{20} unit in hand, a precursory dialdehyde **29** for McMurry coupling was prepared on the basis of our synthetic plan by a method similar to our synthesis of desmethylated analogue of **2**.[4a] Two equivalents of mesylate **25**, derived from the alcohol **24**, was treated with a dialkoxide derived from 1-*O*-benzyl-*sn*-glycerol (**26**)[17] with NaH in DMSO to afford the diether derivative **27** in 56% yield. After deprotection of **27** with diluted HCl in THF, the resulting diol **28** was oxidized to the dialdehyde **29** under Swern conditions in 89% yield.

The key reaction of an intramolecular McMurry coupling of dialdehyde **29** was performed under high dilution conditions. Thus, a solution of dialdehyde **29** in dimethox-

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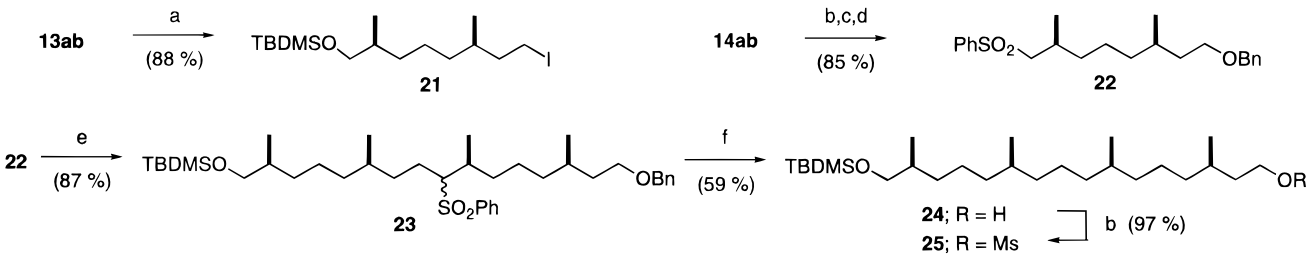
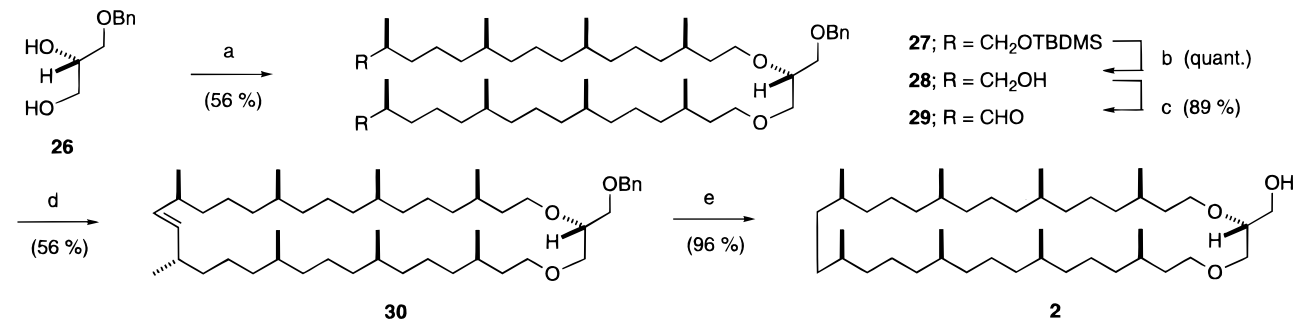
Scheme 3[a]



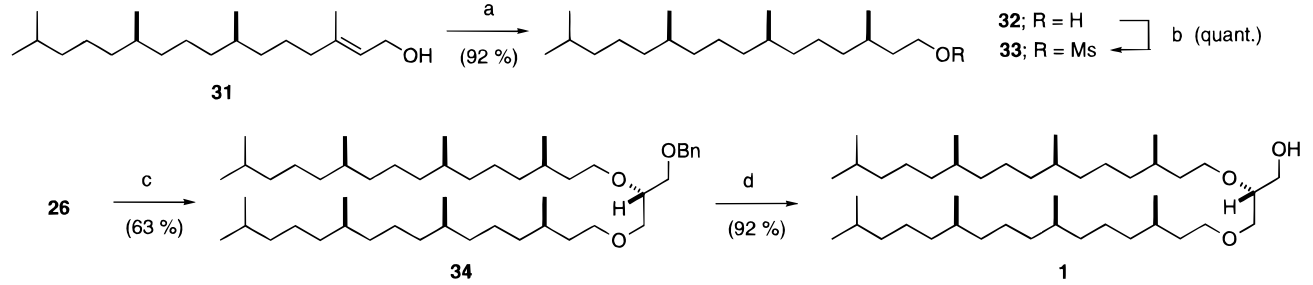
[a] Reagents: (a) I_2, Ph_3P, imidazole/benzene; (b) MsCl/pyridine; (c) PhSH, K_2CO_3/DMF; (d) *m*-CPBA/CH_2Cl_2; (e) (1) ^{n}BuLi/THF−HMPA, (2) compound **21**; (f) Li/$EtNH_2$−THF.

Scheme 4[a]



[a] Reagents: (a) (1) NaH/DMSO, (2) compound **27**; (b) 2 N HCl/THF; (c) Swern oxidation; (d) $TiCl_3$, Zn−Cu/DME; (e) H_2, Pd−C.

Scheme 5[a]



[a] Reagents: (a) H_2, [(*S*)-BINAP]chloro(*p*-cymene)ruthenium chloride/MeOH; (b) MsCl/pyridine; (c) (1) NaH/DMSO, (2) compound **33**; (d) H_2, Pd−C/EtOAc.

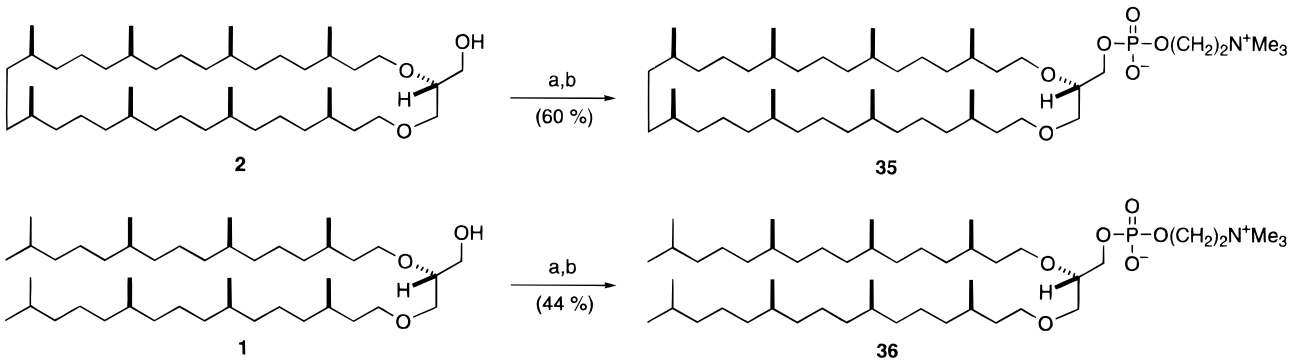
yethane was added by a motor-driven syringe pump over a period of 50−60 h to a refluxing slurry of $TiCl_3$/Zn−Cu in dimethoxyethane to yield the macrocyclic diether **30** as an essentially single product. The best yield we were able to obtain in this coupling reaction was 56%, and the representative yields (50−55%) were obtained from repeated runs. The stereochemistry of the resulting double bond was not rigorously determined but was tentatively assigned to be *E* in analogy with the previous reports that such a macrocyclization by the McMurry coupling reaction predominantly afforded the *E*-double bond.[6] No epimerization at the α-position of carbonyl groups was observed during the McMurry coupling, since degradation of **30** by ozonolysis followed by sodium borohydride reduction afforded material that was identical with **28** in all respects of spectroscopic means. Deprotection of the benzyl group and reduction of the double bond of **30** were performed simultaneously by catalytic hydrogenation over Pd−C to afford the 36-membered diether lipid **2** in 96% yield (Scheme 4).

We were thus successful in synthesizing the archaeal 36-membered diether lipid with branched isoprenoid chains by the McMurry coupling. For detailed investigations of this 36-membered lipid, it is necessary to compare the cyclized lipid with noncyclized counterpart **1**. Although several synthetic studies directing analogues to the archaeal lipid **1** were reported, the chiralities of the C-3 position of the phytanyl moieties and the glycerol part were not taken care of. Surprisingly, nothing has been discussed for the efficient synthesis of stereochemically defined **1**. Therefore, we describe here a highly stereoselective synthetic route to **1** using an asymmetric hydrogenation reaction based on the BINAP−Ru catalyst.[13]

As shown in Scheme 5, the commercially available phytol **31** was hydrogenated in 92% yield into phytanol **32** in the presence of [(*S*)-BINAP]chloro(*p*-cymene)ruthenium chloride. The absolute stereochemistry of the newly formed stereogenic center was determined to be *R* from its optical rotation,[2a] and the diastereomeric purity was 95%.[18] By similar manipulation as described for **2**, phytanol **32** was converted to archaeal core lipid **1** *via* mesylation, etherification with 1-*O*-benzylglycerol,

(18) The diastereomeric excess was determined by the method of Noyori *et al.* (ref 13a).

Scheme 6[a]



[a] Reagents: (a) (1) $Cl_2P(=O)O(CH_2)_2Cl$/pyridine, (2) H_2O; (b) NMe_3/toluene−CH_3CN.

and hydrogenation. Thus, we have achieved the synthesis of archaeal lipid **1** starting from phytol in 53% overall yield.

Our next interest was to focus on the characteristics of the synthetic macrocyclic diether lipid. Therefore, the synthesized archaeal macrocyclic lipid **2** and noncyclized (linear) counterpart **1** were converted into the corresponding phosphocholine derivatives **35** and **36**, respectively. The synthetic lipids **2** and **1** were converted to the phosphodiester derivatives by treatment with an excess of (*β*-chloroethyl)phosphoryl dichloride in pyridine. Subsequent displacement of the chlorine atom by trimethylamine in a pressure bottle for 3 days at 50−60 °C gave the phosphocholine derivatives **35** and **36**. The overall yields of **35** and **36** from **2** and **1** were 60% and 44%, respectively (Scheme 6). Preliminary electron and optical microscopic studies have revealed that vesicles were formed in an aqueous dispersion of the synthesized phosphocholine derivatives **35** and **36** (data not shown). Investigation of the properties of the synthesized lipids are in progress and will be reported in due course.

In summary, a total synthesis of an archaeal 36-membered macrocyclic diether lipid **2** has been achieved by using intramolecular McMurry coupling as a key reaction. In addition, we have developed a highly stereoselective and convenient synthesis of archaeal biphytanyl glycerol lipid **1**. These results may stimulate investigations into the characteristics of the thermophilic archaeal 36-membered macrocyclic diether lipids. Furthermore, extension of this methodology to the synthesis of archaeal 72-membered macrocyclic tetraether lipids is currently underway in our laboratory.

Experimental Section

General Information. All reactions, except for catalytic hydrogenation reactions, were carried out in an inert (Ar or N_2) atmosphere. THF, diethyl ether, and DME were distilled from sodium/benzophenone ketyl prior to use. Pyridine and triethylamine were distilled from potassium hydroxide. DMF was distilled from $CaSO_4$, and benzene, DMSO, CH_2Cl_2, HMPA, and toluene were distilled from calcium hydride. Coupling constants, *J*, are given in Hz.

(3*S*)-4-[(1-Ethoxyethyl)oxy]-3-methylbutanenitrile (5). A mixture of methyl (*R*)-3-hydroxy-2-methylpropionate (**4**) (24.8 g, 0.210 mol, Aldrich), ethyl vinyl ether (30 mL, 0.315 mol), and PPTS (200 mg) in THF (180 mL) was stirred for 2 h at room temperature. To this reaction mixture was added $LiAlH_4$ (7.97 g, 0.210 mol) in small portions at 0 °C, and the mixture was stirred at 0 °C for 1 h. Water was carefully added. The insoluble materials were filtered off and washed with THF. The filtrate and washings were combined and concentrated to dryness. The residual oil was dissolved in pyridine (150 mL), and TsCl (60.0 g, 0.315 mol) was added at 0 °C. The mixture was stirred at room temperature for 15 h. Water and EtOAc were added. The organic phase was separated, and the aqueous phase was extracted with EtOAc. The combined organic phase was successively washed with 2 N HCl, saturated aqueous $NaHCO_3$, and brine, dried (Na_2SO_4), filtered, and concentrated to dryness. The residual oil was dissolved in DMSO (180 mL). NaCN (12.3 g, 0.252 mol) was added, and the solution was stirred at 50 °C for 14 h. Water and EtOAc were added, and the organic phase was separated. The aqueous phase was extracted with EtOAc. The combined organic phase was washed with brine, dried (Na_2SO_4), filtered, and concentrated to dryness. The residue was chromatographed over silica gel with hexane−EtOAc (4:1) to give cyanide **5** (35.1 g, 98%) as an oil. ^{1}H NMR (270 MHz) *δ*: 1.09 (d, *J* = 7.0, 3H), 1.21 (t, *J* = 7.0, 3H), 1.30 (d, *J* = 5.0, 3H), 2.12 (m, 1H), 2.37 (ddd, *J* = 16.8, 6.7, 2.3, 1H), 2.49 (ddd, *J* = 16.8, 5.5, 2.3, 1H), 3.21−3.71 (m, 4H), 4.68 (dt, *J* = 2.3, 4.9, 1/2H), 4.70 (dt, *J* = 2.3, 4.9, 1/2H). IR (neat): 1390, 2250, 2900, 2980 cm^{-1}. Anal. Calcd for $C_9H_{17}NO_2$: C, 63.12; H, 10.01; N, 8.18. Found: C, 63.10; H, 9.73; N, 7.88.

(3*S*)-4-[(*tert*-Butyldimethylsilyl)oxy]-3-methylbutanenitrile (6). A solution of **5** (34.2 g, 0.200 mol) in 2 N HCl (18 mL) and THF (180 mL) was stirred for 2 h at room temperature. Saturated $NaHCO_3$ and EtOAc were added, and the organic phase was separated. The aqueous phase was extracted with EtOAc. The combined organic phase was successively washed with brine, dried (Na_2SO_4), filtered, and concentrated to dryness. The residual oil was dissolved in DMF (90 mL). Imidazole (34.0 g, 0.494 mol) and TBDMSCl (35.4 g, 0.235 mol) were added, and the solution was stirred for 2 h at room temperature. Water and EtOAc were added, and the organic phase was separated. The aqueous phase was extracted with EtOAc. The combined organic phase was washed with brine, dried (Na_2SO_4), filtered, and concentrated to dryness. The residue was chromatographed over silica gel with hexane−EtOAc (20:1) to give TBDMS ether **6** (39.0 g, 92%) as an oil. $[\alpha]^{27}_D$: +22.7° (*c* 5.64, $CHCl_3$). ^{1}H NMR (270 MHz) *δ*: 0.01 (s, 6H), 0.85 (s, 9H), 0.99 (d, *J* = 7.0, 3H), 1.91−2.05 (m, 1H), 2.27 (dd, *J* = 16.3, 6.9, 1H), 2.43 (dd, *J* = 16.3, 5.6, 1H), 3.36 (dd, *J* = 11.1, 7.4, 1H), 3.56 (dd, *J* = 11.1, 4.7, 1H). ^{13}C NMR (67.5 MHz) *δ*: −5.59, −5.54, 15.79, 18.19, 20.85, 25.78, 33.21, 65.98, 118.84. IR (neat): 780, 840, 1100, 1260, 1460, 1750, 2250, 2860, 2950 cm^{-1}. Anal. Calcd for $C_{11}H_{23}NOSi$: C, 61.91; H, 10.86; N, 6.56. Found: C, 61.61; H, 10.58; N, 6.79.

(3*S*)-4-[(*tert*-Butyldimethylsilyl)oxy]-3-methylbutanol (7). A solution of DIBAH in toluene (1.0 M, 33 mL, 33 mmol) was added dropwise to a solution of **6** (6.4 g, 30 mmol) in toluene (50 mL) over 15 min at −78 °C, and the mixture was stirred at −78 °C for 15 min. Saturated aqueous NH_4Cl (9.3 mL) was added, and the mixture was gradually warmed to room temperature. Ether (100 mL) and 2 N HCl (100 mL) were added, and the mixture was allowed to stir at room temperature for 20 min. The organic phase was separated, and the aqueous phase was extracted with ether. The

combined organic phase was successively washed with saturated aqueous $NaHCO_3$ and brine, dried (Na_2SO_4), filtered, and concentrated to dryness. The residue was dissolved in toluene (50 mL), a solution of DIBAH in toluene (1.0 M, 33 mL, 33 mmol) was added dropwise to the solution over 15 min at −78 °C, and the mixture was stirred at −78 °C for 10 min. Saturated aqueous NH_4Cl (9.3 mL) was added, and the mixture was gradually warmed to room temperature. Ether (100 mL) and 2 N HCl (100 mL) were added, and the mixture was allowed to stir at room temperature for 20 min. The organic phase was separated, and the aqueous phase was extracted with ether. The combined organic phase was successively washed with saturated aqueous $NaHCO_3$ and brine, dried (Na_2SO_4), filtered, and concentrated to dryness. The resulting residual oil was chromatographed over silica gel with hexane−EtOAc (5:1) to give alcohol **7** (4.8 g, 73%) as an oil. $[\alpha]^{27}_D$: −6.96° (*c* 4.80, $CHCl_3$). ^{1}H NMR (270 MHz) δ: 0.12 (s, 6H), 0.90 (d, J = 6.9, 3H), 0.91 (s, 9H), 1.58 (m, 2H), 1.78 (m, 1H), 2.84 (br, 1H), 3.43 (dd, J = 9.9, 6.9, 1H), 3.54 (dd, J = 9.9, 4.6, 1H), 3.67 (m, 2H). ^{13}C NMR (67.5 MHz) δ: −5.53, −5.48, 17.27, 18.28, 25.84, 33.89, 37.95, 61.06, 68.75. IR (neat): 780, 840, 1100, 1260, 1460, 2330, 2860, 2950, 3350 cm^{-1}. Anal. Calcd for $C_{11}H_{26}O_2Si$: C, 60.49; H, 12.00. Found: C, 60.51; H, 12.30.

(2*S*)-1-[(*tert*-Butyldimethylsilyl)oxy]-4-iodo-2-methylbutane (8). A mixture of **7** (9.5 g, 43.5 mmol), imidazole (7.4 g, 108.7 mmol), triphenylphosphine (28.5 g, 108.7 mmol), and I_2 (22.1 g, 87.1 mmol) in benzene (300 mL) was stirred for 1 h at room temperature. Saturated aqueous $Na_2S_2O_3$ was added, and the organic phase was separated. The aqueous phase was extracted with EtOAc. The combined organic phase was washed with brine, dried (Na_2SO_4), filtered, and concentrated to dryness. The residue was chromatographed over silica gel with hexane to give iodide **8** (12.1 g, 85%) as an oil. $[\alpha]^{27}_D$: −10.5° (*c* 2.35, $CHCl_3$). ^{1}H NMR (270 MHz) δ: 0.04 (s, 6H), 0.88 (d, J = 5.5, 3H), 0.89 (s, 9H), 1.71 (m, 2H), 2.00 (m, 1H), 3.20 (dt, J = 9.5, 7.2, 1H), 3.28 (ddd, J = 9.5, 7.8, 5.9, 1H), 3.43 (dd, J = 9.2, 5.6, 1H), 3.47 (dd, J = 9.2, 5.6, 1H). ^{13}C NMR (67.5 MHz) δ: −5.42, 5.12, 15.93, 18.26, 25.90, 36.65, 37.58, 67.34. IR (neat): 780, 850, 1100, 1250, 1460, 2850, 2950 cm^{-1}. Anal. Calcd for $C_{11}H_{25}OSiI$: C, 40.24; H, 7.68. Found: C, 40.51; H, 7.98.

(2*S*)-4-(Benzyloxy)-2-methylbutanol (9). A solution of alcohol **7** (9.0 g, 41.2 mmol), benzyl 2,2,2-trichloroacetimidate (15.4 mL, 82.9 mmol), and trifluoromethanesulfonic acid (0.5 mL, 3.3 mmol) in ether (70 mL) was stirred at room temperature for 40 min. Saturated aqueous $NaHCO_3$ was added, and the organic phase was separated. The aqueous phase was extracted with ether. The combined organic phase was washed with brine, dried (Na_2SO_4), filtered, and concentrated to dryness. The residue was dissolved in THF (80 mL), 2 N HCl (50 mL) and methanol (50 mL) were added, and the mixture was stirred at room temperature for 3.5 h. After removal of organic solvent, brine and EtOAc were added, and the organic phase was separated. The aqueous phase was extracted with EtOAc, and the combined organic phase was washed with saturated $NaHCO_3$ and brine, dried (Na_2SO_4), filtered, and concentrated to dryness. The residue was chromatographed over silica gel with hexane−EtOAc (10:1−3:1) to give benzyl ether **9** (7.0 g, 88%) as an oil. $[\alpha]^{27}_D$: −7.85° (*c* 3.07, $CHCl_3$). ^{1}H NMR (270 MHz) δ: 0.92 (d, J = 6.7, 3H), 1.49−1.89 (m, 3H), 2.51 (br, 1H), 3.37−3.63 (m, 4H), 4.51 (s, 2H), 7.23−7.40 (m, 5H). ^{13}C NMR (67.5 MHz) δ: 17.12, 33.96, 34.03, 68.00, 68.63, 73.09, 127.67, 127.70, 128.39, 137.97. IR (neat): 740, 1040, 1100, 1370, 1460, 2880, 2940, 3410 cm^{-1}. Anal. Calcd for $C_{12}H_{18}O_2$: C, 74.19; H, 9.34. Found: C, 73.89; H, 9.35.

(2*S*)-4-(Benzyloxy)-1-(phenylsulfonyl)-2-methylbutane (10). Methanesulfonyl chloride (2.17 mL, 28.0 mmol) was added to a solution of **9** (4.54 g, 23.4 mmol) in pyridine (20 mL) at 0 °C, and the mixture was stirred at room temperature for 3 h. Water and EtOAc were added, and the organic phase was separated. The aqueous phase was extracted with EtOAc. The combined organic phase was successively washed with 2 N HCl, saturated aqueous $NaHCO_3$, and brine, dried (Na_2SO_4), filtered, and concentrated to dryness. The residue was dissolved in DMF (50 mL), and thiophenol (2.88 mL, 28.0 mmol) and K_2CO_3 (3.88 g, 28.0 mmol) were added. The mixture was stirred for 15 min at room temperature. Water was added, and the mixture was extracted with EtOAc. The organic phase was washed with brine, dried (Na_2SO_4), filtered, and concentrated to dryness. To a solution of the resulting residue in CH_2Cl_2 (150 mL) was added *m*-CPBA (14.3 g, 82.9 mmol) at 0 °C, and the mixture was stirred for 1 h at 0 °C. Saturated aqueous $Na_2S_2O_3$ was added, and the organic phase was separated. The aqueous phase was extracted with CH_2Cl_2. The combined organic phase was washed with brine, dried (Na_2SO_4), filtered, and concentrated to dryness. The residue was chromatographed over silica gel with hexane−EtOAc (7:1−3:1) to give sulfone **10** (10.4 g, 89%) as an oil. $[\alpha]^{27}_D$: +2.02° (*c* 4.87, $CHCl_3$). ^{1}H NMR (270 MHz) δ: 1.11 (d, J = 7.0, 3H), 1.55 (m, 1H), 1.77 (m, 1H), 2.28 (m, 1H), 2.95 (dd, J = 14.1, 7.9, 1H), 3.25 (dd, J = 14.1, 4.6, 1H), 3.46 (m, 2H), 4.42 (s, 2H), 7.25−7.37 (m, 5H), 7.47−7.65 (m, 3H), 7.86−7.91 (m, 2H). ^{13}C NMR (67.5 MHz) δ: 19.98, 26.47, 36.19, 62.35, 67.65, 72.91, 127.53, 127.81, 128.28, 128.33, 129.17, 133.43, 138.24, 140.08. IR (neat): 1110, 1150, 1300, 1450, 2860, 2930 cm^{-1}. Anal. Calcd for $C_{12}H_{18}OS$: C, 67.89; H, 6.97. Found: C, 68.12; H, 7.03.

(2*S*,6*S*)-8-(Benzyloxy)-1-[(*tert*-butyldimethylsilyl)oxy]-2,6-dimethyl-5-(phenylsulfonyl)octane (11). A 50 mL Schlenk tube was charged with **10** (588 mg, 1.85 mmol) and degassed THF (10 mL). A solution of *n*-butyllithium in hexane (1.68 M, 1.21 mL, 2.04 mmol) was added dropwise, and the slurry was stirred at −78 °C for 20 min. The mixture was warmed to room temperature and allowed to stir for 10 min. The mixture was recooled to −25 °C. HMPA (4.0 mL) was added, followed by a solution of **8** (606 mg, 1.85 mmol) in degassed THF (4 mL). The mixture was stirred at −25 °C for 1 h and then at room temperature for 1 h. Saturated aqueous NH_4Cl was added, and the mixture was extracted twice with EtOAc. The combined organic phase was washed with brine, dried (Na_2SO_4), filtered, and concentrated to dryness. The residue was chromatographed over silica gel with hexane−EtOAc (10:1) to give sulfone **11** (695 mg, 73%) as an oil. ^{1}H NMR (270 MHz) δ: 0.12 (s, 6H), 0.86 (d, J = 6.6, 3H), 0.96 (s, 9H), 1.14 (d, J = 8.0, 3H), 1.10−2.00 (m, 8H), 3.15 (dt, J = 1.5, 6.8, 1H), 3.32−3.70 (m, 4H), 4.49 (dd, J = 13.5 11.8, 2H), 7.33−7.47 (m, 5H), 7.51−7.72 (m, 3H), 7.94 (m, 2H). IR (neat): 840, 1090, 1150, 1350, 1460, 2850, 2950 cm^{-1}. Anal. Calcd for $C_{29}H_{46}O_4SSi$: C, 67.13; H, 8.94. Found: C, 67.34; H, 9.17.

(2*S*,6*S*)-8-(Benzyloxy)-1-[(*tert*-butyldimethylsilyl)oxy]-2,6-dimethyloctane (12a). A mixture of **11** (3.56 g, 6.86 mmol) and 5% sodium amalgam (41.1 g, 89.3 mmol) in methanol (70 mL) was stirred for 13 h at room temperature. The mixture was filtered, and the residual mercury was washed with EtOAc. The filtrate and washings were combined, washed with brine, dried (Na_2SO_4), filtered, and concentrated to dryness. The residue was chromatographed over silica gel with hexane−EtOAc (40:1−10:1) to give **12a** (2.20 g, 85%) as an oil. $[\alpha]^{27}_D$: +0.44° (*c* 1.75, $CHCl_3$). ^{1}H NMR (300 MHz) δ: 0.03 (s, 6H), 0.86 (d, J = 6.6, 3H), 0.87 (d, J = 6.6, 3H), 0.89 (s, 9H), 0.95−1.73 (m, 10 H), 3.34 (dd, J = 9.5, 6.8, 1H), 3.44 (dd, J = 9.5, 5.9, 1H), 3.49 (t, J = 6.8, 1H), 3.50 (dd, J = 7.2, 6.0, 1H), 4.50 (s, 2H), 7.25−7.34 (m, 5H). ^{13}C NMR (75 MHz) δ: −5.35, 16.79, 18.35, 19.67, 24.27, 25.96, 29.85, 33.43, 35.74, 36.74, 37.43, 68.38, 68.74, 72.88, 127.44, 127.58, 128.31, 138.69. IR (neat): 850, 1110, 2880, 2950 cm^{-1}. Anal. Calcd for $C_{23}H_{42}O_2Si$: C, 72.95; H, 11.18. Found: C, 72.84; H, 11.22.

(3*R*,7*S*)-8-[(*tert*-Butyldimethylsilyl)oxy]-2,6-dimethyl-1-octanol (13a). A mixture of **12a** (1.08 g, 2.85 mmol) and 10% Pd−C (119 mg) in EtOAc (20 mL) was stirred at room temperature under hydrogen atmosphere for 50 h. The catalyst was filtered off and washed with EtOAc. The filtrate and washings were combined and concentrated to dryness. The residue was purified by chromatography over silica gel with hexane−EtOAc (10:1) to give **13a** (0.79 g, 96%) as an oil. $[\alpha]^{27}_D$: −0.49° (*c* 1.73, $CHCl_3$). ^{1}H NMR (300 MHz) δ: 0.04 (s, 6H), 0.87 (d, J = 6.6, 3H), 0.89 (d, J = 6.4, 3H), 0.90 (s, 9H), 1.00−1.67 (m, 10H), 3.35 (dd, J = 9.8, 6.4, 1H), 3.44 (dd, J = 9.8, 5.5, 1H), 3.68 (m, 2H). ^{13}C NMR (75 MHz) δ: −5.36, 16.76,

18.35, 19.64, 24.26, 25.94, 29.45, 33.40, 35.73, 37.43, 39.91, 61.21, 68.37. IR (neat): 840, 1100, 2860, 2940, 2960, 3350 cm^{-1}. Anal. Calcd for $C_{16}H_{36}O_2Si$: C, 66.60; H, 12.58. Found: C, 66.52; H, 12.86.

(2*S*,6*R*)-8-(Benzyloxy)-2,6-dimethyloctanol (14a). A mixture of **12a** (1.09 g, 2.88 mmol) and 2 N HCl (1 mL) in THF (5 mL) and methanol (3 mL) was stirred for 1.5 h at room temperature. Saturated aqueous $NaHCO_3$ and EtOAc were added, the organic phase was separated, and the aqueous phase was extracted with EtOAc. The combined organic layer was washed with brine, dried (Na_2SO_4), filtered, and concentrated to dryness. The residue was chromatographed over silica gel with hexane−EtOAc (10:1−2:1) to give **14a** (0.60 g, 79%) as an oil. $[\alpha]^{28}_D$: −4.81° (*c* 1.10, $CHCl_3$). ^{1}H NMR (300 MHz) δ: 0.86 (d, J = 6.6, 3H), 0.88 (d, J = 6.6, 3H), 0.96−1.73 (m, 10H), 2.73 (br, 1H), 3.31 (dd, J = 10.2, 6.6, 1H), 3.41 (dd, J = 10.2, 5.9, 1H), 3.47 (t, J = 7.1, 1H), 3.48 (dd, J = 7.1, 6.0, 1H), 4.47 (s, 2H), 7.22−7.32 (m, 5H). ^{13}C NMR (75 MHz) δ: 16.58, 19.66, 24.21, 29.81, 33.35, 35.71, 36.67, 37.33, 68.27, 68.69, 72.86, 127.44, 127.58, 128.30, 138.64. IR (neat): 1100, 1460, 2860, 2940, 3380 cm^{-1}. Anal. Calcd for $C_{17}H_{28}O_2$: C, 77.22; H, 10.67. Found: C, 77.48; H, 10.94.

(4*R*)-6-(Benzyloxy)-4-methylhexanol (17). Ozone gas was introduced into a solution of **16**[14] (17.9 g, 72.6 mmol) in methanol (30 mL) at −78 °C for 10 h. $NaBH_4$ (3.0 g, 79.3 mmol) was carefully added to the mixture at −78 °C, and the mixture was gradually warmed to room temperature. The solvent was removed, and the residue was diluted with ether and 2 N HCl. The aqueous phase was extracted with ether. The combined organic phase was successively washed with saturated $NaHCO_3$ and brine, dried (Na_2SO_4), filtered, and concentrated to dryness. The residue was chromatographed over silica gel with hexane−EtOAc (4:1−2:1) to give alcohol **17** (15.1 g, 93%) as an oil. $[\alpha]^{30}_D$: +1.41° (*c* 0.92, $CHCl_3$). ^{1}H NMR (300 MHz) δ: 0.90 (d, J = 6.6, 3H), 1.10−1.75 (m, 7H), 3.50 (t, J = 6.8, 1H), 3.51 (dd, J = 6.8, 6.1, 1H), 3.62 (t, J = 6.6, 2H), 4.50 (s, 2H), 7.26−7.35 (m, 5H). ^{13}C NMR (75 MHz) δ: 19.46, 29.51, 29.98, 32.82, 36.53, 62.94, 68.43, 72.79, 127.43, 127.56, 128.25, 138.37. IR (neat): 698, 737, 1099, 1365, 1454, 2866, 2931, 3373 cm^{-1}. Anal. Calcd for $C_{14}H_{22}O_2$: C, 75.63; H, 9.97. Found: C, 75.35; H, 10.04.

(7*R*)-9-(Benzyloxy)-7-methyl-2-nonyn-1-ol (18). To a solution of **17** (32.0 g, 144 mmol) in pyridine (60 mL) was added *p*-TsCl (35.5 g, 186 mmol) at 0 °C, and the mixture was stirred for 3.5 h at 0 °C. Water was added, and the mixture was extracted with EtOAc. The organic phase was successively washed with 2 N HCl, saturated aqueous $NaHCO_3$, and brine, dried (Na_2SO_4), filtered, and concentrated to dryness to give a crude tosylate (52.5 g). A suspension of prewashed NaH (5.2 g, 217 mmol) in DMSO (104 mL) was heated at 70 °C for 30 min, and the resulting solution was cooled to room temperature. Tetrahydro-2-(2-propynyloxy)-2*H*-pyran (30.5 g, 217 mmol) was added, and the mixture was stirred for 25 min at room temperature. A solution of the crude tosylate (52.5 g) in DMSO (35 mL) was added dropwise over 15 min at 10 °C, and the resulting mixture was stirred for 5 min at 10 °C. Water was added, and the mixture was extracted four times with hexane. The combined organic phase was washed with water, dried (Na_2SO_4), filtered, and concentrated to dryness. The residue was treated with 2 N HCl (16 mL) in THF−methanol (1:1, 200 mL). After removal of the solvent, the residual oil was applied to chromatography over silica gel with hexane−EtOAc (5:1−2:1) to give **18** (26.7 g, 71%) as an oil. $[\alpha]^{28}_D$: +6.21° (*c* 1.10, $CHCl_3$). ^{1}H NMR (300 MHz) δ: 0.88 (d, J = 6.3, 3H), 1.22 (m, 1H), 1.34−1.72 (m, 6H), 2.10 (br, 1H), 2.18 (tt, J = 2.2, 7.1, 2H), 3.49 (t, J = 6.8, 1H), 3.50 (dd, J = 6.8, 6.1, 1H), 4.20 (dt, J = 5.5, 2.0, 2H), 4.50 (s, 2H), 7.25−7.34 (m, 5H). ^{13}C NMR (100 MHz) δ: 18.94, 19.50, 25.94, 29.38, 36.18, 36.58, 51.34, 68.48, 72.87, 78.39, 86.46, 127.49, 127.60, 128.33, 138.54. IR (neat): 698, 737, 1016, 1097, 1365, 1454, 2224, 2285, 2864, 2927, 3386 cm^{-1}. Anal. Calcd for $C_{17}H_{24}O_2$: C, 78.42; H, 9.29. Found: C, 78.12; H, 9.03.

(2*E*,7*R*)-9-(Benzyloxy)-7-methyl-2-nonen-1-ol (19). A solution of **18** (27.0 g, 104 mmol) in THF (40 mL) was added dropwise to a suspension of $LiAlH_4$ (4.1 g, 108 mmol) in THF (130 mL) at 10 °C over 20 min. The mixture was stirred at room temperature for 3 h and then at 50 °C for 4.5 h. Water was carefully added, and the mixture was diluted with ether and 2 N HCl. The organic phase was separated, and the aqueous phase was extracted with ether. The combined organic layer was washed with saturated $NaHCO_3$ and brine, dried (Na_2SO_4), filtered, and concentrated to dryness. The residue was chromatographed over silica gel with hexane−EtOAc (4:1) to give allylic alcohol **19** (25.6 g, 94%) as an oil. $[\alpha]^{28}_D$: +3.63° (*c* 1.17, $CHCl_3$). ^{1}H NMR (300 MHz) δ: 0.87 (d, J = 6.6, 3H), 1.07−1.20 (m, 1H), 1.24−1.67 (m, 6H), 2.02 (m, 2H), 3.49 (t, J = 6.8, 1H), 3.50 (dd, J = 6.8, 6.1, 1H), 4.08 (d, J = 4.9, 2H), 4.50 (s, 2H), 5.62 (dt, J = 4.9, 15.3, 1H), 5.69 (dt, J = 5.6, 15.1, 1H), 7.26−7.35 (m, 5H). ^{13}C NMR (100 MHz) δ: 19.56, 26.42, 29.67, 32.41, 36.53, 36.68, 63.80, 68.59, 72.85, 127.46, 127.59, 128.32, 128.87, 133.42, 138.61. IR (neat): 698, 737, 970, 1003, 1095, 1365, 1454, 1670, 2858, 2927, 3383 cm^{-1}. Anal. Calcd for $C_{17}H_{26}O_2$: C, 77.82; H, 9.99. Found: C, 77.53; H, 10.01.

(2*R*,3*R*,7*R*)-9-(Benzyloxy)-2,3-epoxy-7-methylnonanol (20). To a suspension of molecular sieves 4A powder (22.9 g) in freshly distilled CH_2Cl_2 (390 mL) was added tetraisopropyl orthotitanate (14.0 mL, 47.8 mmol) and D-(−)-diethyl tartrate (10.0 mL, 58.4 mmol) at −25 °C, and the mixture was stirred at −25 °C for 55 min. A solution of **19** (12.3 g, 46.9 mmol) in freshly distilled CH_2Cl_2 (50 mL) was added dropwise at −25 °C over 15 min. After 20 min, *tert*-butyl hydroperoxide in decane (5.5 M, 18.0 mL, 99.0 mmol) was added at −25°C over 10 min, and the mixture was stirred for 1.5 h at −25 °C. Aqueous 10% tartaric acid (200 mL) was added, and the mixture was stirred at room temperature for 1 h. The mixture was diluted with EtOAc, and the organic phase was separated. The aqueous phase was extracted with EtOAc. The combined organic layer was washed with brine, dried (Na_2SO_4), filtered, and concentrated to dryness. The residue was dissolved in ether (160 mL), and 10% aqueous NaOH (80 mL) was added at 0 °C. After 1 h of stirring at 0 °C, two phases were separated, and the aqueous phase was extracted with ether. The combined organic layer was washed with brine, dried (Na_2SO_4), filtered, and concentrated to dryness. The residue was chromatographed over silica gel with hexane−EtOAc (2:1) to give epoxide **20** (11.9 g, 91%) as an oil. $[\alpha]^{26}_D$: +22.19° (*c* 1.50, $CHCl_3$). ^{1}H NMR (300 MHz) δ: 0.88 (d, J = 6.3, 3H), 1.10−1.73 (m, 9H), 2.46 (t, J = 6.3, 1H), 2.90 (m, 2H), 3.49 (t, J = 6.8, 1H), 3.50 (dd, J = 6.8, 6.1, 1H), 3.57 (ddd, J = 12.5, 6.5, 4.7, 1H), 3.85 (ddd, J = 12.5, 5.9, 2.5, 1H), 4.49 (s, 2H), 7.23−7.38 (m, 5H). ^{13}C NMR (75 MHz) δ: 19.38, 23.14, 29.59, 31.62, 36.49, 36.56, 55.87, 58.49, 61.67, 68.41, 72.73, 127.35, 127.48, 128.19, 138.42. IR (neat): 698, 739, 1028, 1099, 1365, 1454, 2862, 2929, 3423 cm^{-1}. Anal. Calcd for $C_{17}H_{26}O_3$: C, 73.35; H, 9.41. Found: C, 73.25; H, 9.61.

(2*S*,6*R*)-8-(Benzyloxy)-2,6-dimethyloctanol (14b). A solution of trimethylaluminum in hexane (1 M, 165 mL, 165 mmol) was added dropwise to a solution of **20** (14.7 g, 52.8 mmol) in CH_2Cl_2 (190 mL) at 0 °C during 15 min, and the mixture was stirred for 3.5 h at 0 °C. Methanol (30 mL) was carefully added, and the mixture was diluted with ether and 2 N HCl. The organic layer was separated, and the aqueous phase was extracted with ether. The combined organic layer was successively washed with saturated aqueous $NaHCO_3$ and brine, dried (Na_2SO_4), filtered, and concentrated to dryness. The residue was dissolved in THF (40 mL) and water (20 mL), and sodium periodate (14.1 g, 65.9 mmol) was added. The resulting mixture was stirred for 2.5 h at room temperature. The mixture was diluted with EtOAc and brine, and the two phases were separated. The aqueous phase was extracted with EtOAc. The combined organic layer was washed with brine, dried (Na_2SO_4), filtered, and concentrated to dryness. The residual oil was dissolved in methanol (75 mL), and $NaBH_4$ (2.1 g, 55.5 mmol) was added at 0 °C. After 1 h of stirring at 0 °C, the solvent was removed *in vacuo*, and the residue was diluted with ether and 2 N HCl. The organic layer was successively washed with saturated $Na_2S_2O_3$, saturated $NaHCO_3$, and brine, dried (Na_2SO_4), filtered, and concentrated to dryness. The residue was chromatographed over silica gel with hexane−EtOAc (7:1−5:1) to give alcohol **14b** (11.8 g, 84%) as an oil.

(2*S*,6*S*)-8-(Benzyloxy)-1-[(*tert*-butyldimethylsilyl)oxy]-2,6-dimethyloctane (12b). A mixture of **14b** (10.0 g, 37.8 mmol), TBDMSCl (7.0 g, 46.4 mmol), and imidazole (6.5 g, 95.5 mmol) in DMF (80 mL) was stirred for 1.5 h at room temperature. Water was added, and the mixture was extracted several times with hexane. The combined organic layer was washed with brine, dried (Na_2SO_4), filtered, and concentrated to dryness. The residue was chromatographed over silica gel with hexane−EtOAc (10:1) to give **12b** (14.1 g, 99%) as an oil.

(3*R*,7*S*)-8-[(*tert*-Butyldimethylsilyl)oxy]-2,6-dimethyl-1-octanol (13b). By the same manner as described for the synthesis of **13a**, compound **12b** (14.1 g, 37.2 mmol) was converted to **13b** (11.0 g, 97%) as an oil.

(2*S*,6*R*)-1-[(*tert*-Butyldimethylsilyl)oxy]-8-iodo-2,6-dimethyloctane (21). A mixture of **13ab** (1.57 g, 5.44 mmol), imidazole (0.92 g, 13.5 mmol), triphenylphosphine (3.55 g, 13.5 mmol), and iodine (2.75 g, 10.8 mmol) in benzene (60 mL) was stirred at room temperature for 30 min. Saturated aqueous $Na_2S_2O_3$ was added, and the mixture was extracted with EtOAc. The organic layer was successively washed with brine, dried (Na_2SO_4), filtered, and concentrated to dryness. The residue was chromatographed over silica gel with hexane−EtOAc (50:1) to give iodide **21** (2.00 g, 92%) as an oil. $[\alpha]^{28}_D$: −9.08° (*c* 1.44, $CHCl_3$). ^{1}H NMR (300 MHz) δ: 0.04 (s, 6H), 0.86 (d, J = 6.8, 3H), 0.87 (d, J = 6.4, 3H), 0.89 (s, 9H), 0.95−1.43 (m, 7H), 1.55 (br, 1H), 1.63 (m, 1H), 1.87 (m, 1H), 3.16 (ddd, J = 9.8, 7.8, 7.1, 1H), 3.25 (ddd, J = 9.8, 7.8, 5.4, 1H), 3.35 (dd, J = 9.8, 6.3, 1H), 3.44 (dd, J = 9.8, 5.9, 1H). ^{13}C NMR (75 MHz) δ: −5.34, 5.40, 16.77, 18.36, 18.74, 24.14, 25.96, 33.35, 33.83, 35.71, 36.55, 40.90, 68.35. IR (neat): 780, 840, 1090, 1250, 1460, 2850, 2930 cm^{-1}. Anal. Calcd for $C_{16}H_{35}OSiI$: C, 48.23; H, 8.85. Found: C, 48.03; H, 8.99.

(2*S*,6*R*)-8-(Benzyloxy)-1-(phenylsulfonyl)-2,6-dimethyloctane (22). A mixture of **14ab** (11.0 g, 41.6 mmol) and methanesulfonyl chloride (4.0 mL, 51.6 mmol) in pyridine (30 mL) was stirred for 3.5 h at 0 °C. Water was added, and the mixture was extracted with EtOAc. The organic phase was successively washed with 2 N HCl, saturated aqueous $NaHCO_3$ and brine, dried (Na_2SO_4), filtered, and concentrated to dryness. The resulting residue was dissolved in DMF (100 mL), and K_2CO_3 (5.9 g, 42.7 mmol) and thiophenol (5.2 mL, 51.0 mmol) were added to the mixture, which was further stirred for 4 h at room temperature. Water was added, and the mixture was extracted four times with hexane. The combined organic layer was washed with brine, dried (Na_2SO_4), filtered, and concentrated to dryness. The residual oil was treated with *m*-CPBA (25.0 g (85%), 123 mmol) in CH_2Cl_2 (120 mL) for 7 h at 0 °C. Saturated aqueous $Na_2S_2O_3$ (150 mL) was added, and the mixture was extracted with EtOAc. The organic layer was successively washed with 10% aqueous NaOH and brine, dried (Na_2SO_4), filtered, and concentrated to dryness. The residue was chromatographed over silica gel with hexane−EtOAc (20:1) to give sulfone **22** (15.4 g, 95%) as an oil. $[\alpha]^{30}_D$: +3.49° (*c* 1.69, $CHCl_3$). ^{1}H NMR (300 MHz) δ: 0.83 (d, J = 6.6, 3H), 1.06 (d, J = 6.6, 3H), 1.14−1.43 (m, 7H), 1.46−1.73 (m, 2H), 2.07 (m, 1H), 2.91 (dd, J = 14.1, 7.8, 1H), 3.07 (dd, J = 14.1, 4.6, 1H), 3.47 (t, J = 6.9, 1H), 3.48 (dd, J = 6.9, 5.7, 1H), 4.48 (s, 2H), 7.26−7.34 (m, 5H), 7.52−7.63 (m, 3H), 7.89−7.92 (m, 2H). ^{13}C NMR (75 MHz) δ: 19.48, 19.84, 23.54, 28.44, 29.60, 36.52, 36.72, 36.81, 62.38, 68.46, 72.78, 127.38, 127.49, 127.72, 128.23, 129.15, 133.42, 138.52, 140.03. IR (neat): 534, 567, 600, 1088, 1147, 1306, 1446, 2858, 2927 cm^{-1}. Anal. Calcd for $C_{23}H_{32}O_3S$: C, 71.09; H, 8.30. Found: C, 70.93; H, 8.48.

(2*S*,6*R*,10*S*,14*R*)-16-(Benzyloxy)-1-[(*tert*-butyldimethylsilyl)oxy]-2,6,10,14-tetramethyl-8-(phenylsulfonyl)hexadecane (23). A 300 mL Schlenk tube was charged with sulfone (**22**) (3.30 g, 8.49 mmol) and degassed THF (50 mL). A solution of *n*-butyllithium in hexane (1.57 M, 5.60 mL, 8.79 mmol) was added dropwise, and the slurry was stirred at −78 °C for 15 min. The mixture was stirred at 0 °C for 15 min and recooled to −25 °C. HMPA (20 mL) was added to the mixture. After 5 min, a solution of iodide **21** (3.38 g, 8.49 mmol) in degassed THF (25 mL) was added over 10 min at −25 °C, and the mixture was stirred at the same temperature for 1 h. Saturated aqueous NH_4Cl was added, and the mixture was extracted with EtOAc. The organic phase was successively washed with saturated $NaHCO_3$ and brine, dried (Na_2SO_4), filtered, and concentrated to dryness. The residue was chromatographed over silica gel with hexane−EtOAc (20:1−10:1) to give sulfone **23** (4.89 g, 87%) as an oil. ^{1}H NMR (300 MHz) δ: 0.04 (s, 6H), 0.77 (d, J = 6.3, 3H), 0.82 (d, J = 6.3, 3H), 0.85 (d, J = 6.6, 3H), 0.90 (s, 9H), 1.01 (d, J = 7.1, 3H), 0.93−1.90 (m, 22H), 2.20 (m, 1H), 2.87 (dt, J = 1.7, 5.6, 1H), 3.34 (dd, J = 9.8, 6.6, 1H), 3.42 (dd, J = 9.8, 5.7, 1H), 3.48 (m, 2H), 4.49 (s, 2H), 7.22−7.37 (m, 5H), 7.58 (m, 3H), 7.88 (m, 2H). IR (neat): 840, 1080, 1140, 1250, 1300, 1460, 2850, 2920 cm^{-1}. Anal. Calcd for $C_{39}H_{66}O_4SSi$: C, 71.07; H, 10.09. Found: C, 71.29; H, 10.29.

(3*R*,7*R*,11*S*,15*S*)-16-[(*tert*-Butyldimethylsilyl)oxy]-3,7,11,15-tetramethylhexadecanol (24). A small portion of Li (80 mg, 10 mmol) was added to a solution of **23** (130 mg, 0.20 mmol) in THF (5 mL) and ethylamine (10 mL) at −78 °C, and the mixture was stirred at −78 °C for 2 h. The excess Li was destroyed by addition of isoprene and methanol. The mixture was diluted with brine and extracted with EtOAc. The organic layer was successively washed with 2 N HCl, saturated $NaHCO_3$, and brine, dried (Na_2SO_4), filtered, and concentrated to dryness. The residue was chromatographed over silica gel with hexane−EtOAc (10:1) to give **24** (50 mg, 59%) as an oil. $[\alpha]^{28}_D$: +0.45° (*c* 1.38, $CHCl_3$). ^{1}H NMR (300 MHz) δ: 0.04 (s, 6H), 0.82−0.91 (m, 12H), 0.90 (s, 9H), 1.00−1.68 (m, 24H), 3.35 (dd, J = 9.8, 6.6, 1H), 3.45 (dd, J = 9.8, 5.8, 1H), 3.69 (m, 2H). ^{13}C NMR (75 MHz) δ: −5.36, 16.79, 18.34, 19.66, 19.76, 24.35, 24.39, 24.43, 25.95, 29.51, 32.73, 32.78, 33.50, 35.74, 37.30, 37.36, 37.48, 39.93, 61.18, 68.43. IR (neat): 760, 840, 1090, 1250, 1460, 2850, 2920, 3340 cm^{-1}. Anal. Calcd for $C_{26}H_{56}O_2Si$: C, 72.83; H, 13.16. Found: C, 72.55; H, 13.14.

1-*O*-Benzyl-2,3-bis-*O*-[(3*R*,7*R*,11*S*,15*S*)-16-[(*tert*-butyldimethylsilyl)oxy]-3,7,11,15-tetramethylhexadecanyl]-*sn*-glycerol (27). Methanesulfonyl chloride (1.00 mL, 12.9 mmol) was added to a mixture of **24** (4.42 g, 10.3 mmol) in pyridine (25 mL) at 0 °C, and the solution was stirred at 0 °C for 2.5 h. Water (60 mL) was added, and the mixture was extracted with EtOAc. The organic phase was successively washed with 2 N HCl, saturated aqueous $NaHCO_3$, and brine, dried (Na_2SO_4), filtered, and concentrated to dryness. The methanesulfonate residue was used for the next step without further purification. To a suspension of prewashed NaH (104 mg, 4.33 mmol) in DMSO (2 mL) was added a solution of 1-*O*-benzyl-*sn*-glycerol (**26**) (213 mg, 1.17 mmol) in DMSO (3 mL) at room temperature. The mixture was stirred at room temperature for 1 h, and a solution of mesylate (1.24 g, 2.45 mmol) in DMSO (14 mL) was added at room temperature. The mixture was stirred at room temperature for 2 days. Water was added, and the mixture was extracted with EtOAc. The organic phase was washed with water, dried (Na_2SO_4), filtered, and concentrated to dryness. The residue was chromatographed over silica gel with hexane−EtOAc (20:1) to give **27** (656 mg, 56%) as an oil. $[\alpha]^{26}_D$: +0.68° (*c* 1.56, $CHCl_3$). ^{1}H NMR (300 MHz) δ: 0.04 (s, 12H), 0.83−0.90 (m, 24H), 0.89 (s, 18H), 0.94−1.73 (m, 48H), 3.32−3.64 (m, 13H), 4.55 (s, 2H), 7.26−7.34 (m, 5H). ^{13}C NMR (67.5 MHz) δ: −5.34, 16.81, 18.35, 19.69, 19.71, 19.76, 24.39, 24.48, 25.97, 29.81, 29.90, 29.94, 32.76, 32.82, 33.52, 35.76, 36.64, 37.10, 37.41, 37.53, 68.42, 68.87, 69.97, 70.31, 70.78, 73.35, 77.95, 127.48, 127.57, 128.29, 138.42. IR (neat): 780, 840, 1090, 1250, 1460, 2850, 2920 cm^{-1}. Anal. Calcd for $C_{62}H_{122}O_5Si_2$: C, 74.18; H, 12.25. Found: C, 74.31; H, 12.27.

1-*O*-Benzyl-2,3-bis-*O*-[(3*R*,7*R*,11*S*,15*S*)-16-hydroxy-3,7,11,15-tetramethylhexadecanyl]-*sn*-glycerol (28). A mixture of **27** (51 mg, 0.051 mmol) and 2 N HCl (0.3 mL) in THF (3 mL) was stirred for 5 h at room temperature. Saturated aqueous $NaHCO_3$ was added, and the mixture was extracted with EtOAc. The organic layer was washed with brine, dried (Na_2SO_4), filtered, and concentrated to dryness. The residue was chromatographed over silica gel with hexane−EtOAc (4:1) to give diol **28** (40.0 mg, quantitative) as an oil. $[\alpha]^{28}_D$: −2.45° (*c* 0.86, $CHCl_3$). ^{1}H NMR (300 MHz) δ: 0.84 (d, J = 6.8, 6H), 0.85 (d, J = 6.3, 6H), 0.87 (d, J = 6.6, 6H), 0.91 (d, J = 6.8, 6H), 0.96−1.70 (m, 48H), 1.80 (br, 2H), 3.36−3.64 (m, 13H), 4.55 (s, 2H), 7.26−7.34 (m, 5H). ^{13}C NMR (75 MHz) δ:

16.61, 19.64, 19.66, 19.72, 24.31, 24.35, 24.37, 29.75, 29.83, 32.69, 32.73, 33.44, 35.71, 36.56, 37.02, 37.26, 37.31, 37.46, 37.47, 68.22, 68.82, 69.91, 70.23, 70.72, 73.29, 77.88, 127.44, 127.53, 128.24, 138.33. IR (neat): 1040, 1120, 1380, 1460, 2850, 2920, 3400 cm^{-1}. Anal. Calcd for $C_{50}H_{94}O_5$: C, 77.46; H, 12.22. Found: C, 77.41; H, 12.51.

1-*O*-Benzyl-2,3-bis-*O*-[(3*R*,7*R*,11*S*,15*S*)-16-formyl-3,7,-11,15-tetramethylhexadecanyl]-*sn*-glycerol (29). Dimethyl sulfoxide (180 μL, 2.54 mmol) was added to a solution of $(COCl)_2$ (2 M in CH_2Cl_2, 1.00 mL, 2.00 mmol) in CH_2Cl_2 (11 mL) at −78 °C, and the mixture was stirred at the same temperature for 35 min. To this mixture was added dropwise a solution of **28** (299 mg, 0.386 mmol) in CH_2Cl_2 (9 mL) at −78 °C. The mixture was stirred at −78 °C for 20 min and then at −25 °C for 2 h. The mixture was recooled to −78 °C, and Et_3N (0.90 mL, 6.5 mmol) was added dropwise. The reaction mixture was gradually warmed to room temperature. Water was added, and the mixture was extracted with EtOAc. The organic layer was successively washed with 2 N HCl, saturated aqueous $NaHCO_3$, and brine, dried (Na_2SO_4), filtered, and concentrated to dryness. The residue was purified by flash chromatography over silica gel with hexane−EtOAc (20:1) to give **29** (264 mg, 89%) as an oil. $[\alpha]^{26}_D$: +10.81° (*c* 1.30, $CHCl_3$). ^{1}H NMR (300 MHz) δ: 0.84 (d, J = 7.8, 6H), 0.85 (d, J = 6.3, 6H), 0.87 (d, J = 6.1, 6H), 1.09 (d, J = 7.1, 6H), 0.99−1.75 (m, 46H), 2.34 (m, 2H), 3.44−3.65 (m, 9H), 4.55 (s, 2H), 7.27−7.34 (m, 5H), 9.61 (d, J = 2.0, 2H). ^{13}C NMR (75 MHz) δ: 13.34, 19.63, 19.66, 19.70, 19.73, 24.34, 24.39, 24.43, 29.67, 29.80, 29.87, 30.84, 32.63, 32.78, 36.61, 36.98, 37.07, 37.31, 37.35, 37.41, 37.50, 46.33, 68.86, 69.94, 70.28, 70.76, 73.32, 77.92, 127.47, 127.55, 128.27, 138.40, 205.40. IR (neat): 1120, 1380, 1460, 1730, 2850, 2930 cm^{-1}. Anal. Calcd for $C_{50}H_{90}O_5$: C, 77.87; H, 11.76. Found: C, 77.78; H, 11.81.

(2*S*,7*R*,11*R*,15*S*,19*S*,22*S*,26*S*,30*R*,34*R*)-2-(Benzyloxymethyl)-7,11,15,19,22,26,30,34-octamethyl-1,4-dioxacyclohexatriacont-20-ene (30). Powdered $TiCl_3$ (1.0 g, 6.5 mmol) and Zn−Cu couple (1.0 g, 15.4 mmol) were placed in a 200 mL Schlenk tube. DME (50 mL) was added, and the mixture was refluxed for 1.5 h. A solution of **29** (264 mg, 0.343 mmol) in DME (50 mL) was added to the refluxing slurry *via* a motor-driven syringe pump over a 50 h period. After an additional 18 h of refluxing, the reaction mixture was cooled to room temperature. The mixture was treated with 20% aqueous K_2CO_3 (70 mL) at room temperature for 3 h and then extracted with EtOAc. The organic layer was washed with brine, dried (Na_2SO_4), filtered, and concentrated to dryness. The residue was purified by flash chromatography over silica gel with hexane−EtOAc (25:1) to give **30** (141 mg, 56%) as an oil. $[\alpha]^{23}_D$: +6.66° (*c* 1.16, $CHCl_3$). ^{1}H NMR (300 MHz) δ: 0.83 (d, J = 6.3, 6H), 0.84 (d, J = 6.3, 6H), 0.87 (d, J = 6.6, 6H), 0.94 (d, J = 6.8, 6H), 0.98−1.70 (m, 46H), 2.02 (br, 2H), 3.45−3.65 (m, 9H), 4.55 (s, 2H), 5.11 (m, 2H), 7.25−7.34 (m, 5H). ^{13}C NMR (75 MHz) δ: 19.77, 19.85, 21.82, 24.48, 25.05, 29.60, 29.72, 32.75, 32.83, 32.87, 36.64, 36.98, 37.23, 37.36, 37.46, 37.47, 37.76, 68.58, 69.70, 70.28, 71.43, 73.35, 77.94, 127.50, 127.57, 128.30, 134.97, 138.37. IR (neat): 696, 733, 968, 1117, 1377, 1462, 2858, 2925 cm^{-1}. EI-MS m/z: 738 (M^+), 647, 632, 555. High-resolution EI-MS: calcd for $C_{50}H_{90}O_3$ 738.6890, found 738.6918. Anal. Calcd for $C_{50}H_{90}O_3$: C, 81.24; H, 12.27. Found: C, 81.31; H, 12.49.

(2*R*,7*R*,11*R*,15*S*,19*S*,22*S*,26*S*,30*R*,34*R*)-2-(Hydroxymethyl)-7,11,15,19,22,26,30,34-octamethyl-1,4-dioxacyclohexatriacontane (2). A mixture of **30** (80 mg, 0.11 mmol) and 10% Pd−C (80 mg) in EtOAc (5 mL) was stirred for 3 days under hydrogen atmosphere at room temperature. The catalyst was filtered through a pad of Celite and washed with EtOAc. The filtrate and washings were combined and concentrated to dryness. The residue was purified by flash chromatography over silica gel with hexane−EtOAc (10:1) to give **2** (68 mg, 96%) as an oil. $[\alpha]^{26}_D$: +8.17° (*c* 1.16, $CHCl_3$). ^{1}H NMR (300 MHz) δ: 0.84−0.89 (m, 24H) 1.00−1.68 (m, 52H), 2.20 (br, 1H), 3.46−3.73 (m, 9H). ^{13}C NMR (75 MHz) δ: 19.76, 1985, 19.93, 19.97, 20.02, 20.08, 23.96, 24.26, 24.34, 24.42, 29.72, 29.77, 32.41, 32.46, 32.50, 32.59, 32.66, 32.77, 33.03, 33.56, 34.16, 36.53, 36.67, 36.90, 36.99, 37.17, 37.19, 37.26, 63.02, 68.52, 70.00, 71.18, 71.23, 78.37. IR (neat): 1050, 1110, 1380, 1460, 2850, 2920, 3440 cm^{-1}. EI-MS m/z: 650 (M^+), 620, 557. High-resolution EI-MS: calcd for $C_{43}H_{86}O_3$ 650.6577, found 650.6603. Anal. Calcd for $C_{43}H_{86}O_3$: C, 79.32; H, 13.31. Found: C, 79.60; H, 13.31.

(3*R*,7*R*,11*R*)-3,7,11,15-Tetramethylhexadecan-1-ol (Phytanol) (32). A mixture of phytol (**31**) (12.9 g, 43.5 mmol) and [(*S*)-(−)-2,2′-bis(diphenylphosphino)-1,1′-binaphthyl]chloro(*p*-cymene)ruthenium chloride (97 mg) in degassed methanol (40 mL) was placed in a stainless steel autoclave under argon atmosphere. High purity hydrogen gas (99.999 99% purity) was introduced into the reaction apparatus (90 kgf/cm^2). The mixture was stirred at room temperature for 4 days. The mixture was concentrated *in vacuo*, and the residue was chromatographed over silica gel with hexane−EtOAc (10:1) to give phytanol (**32**) (11.9 g, 92%) as an oil. $[\alpha]^{29}_D$: +2.29° (*c* 1.02, $CHCl_3$) (lit.[2a] $[\alpha]^{29}_D$ +2.4°). ^{1}H NMR (300 MHz) δ: 0.84−0.91 (d, J = 6.6, 15H) 1.00−1.67 (m, 25H), 3.62−3.75 (m, 2H). ^{13}C NMR (75 MHz) δ: 19.66, 19.74, 19.76, 22.62, 22.72, 24.35, 24.44, 24.78, 27.96, 29.49, 32.78, 37.26, 37.29, 37.36, 37.42, 37.47, 39.34, 39.93, 61.24. IR (neat): 737, 760, 1009, 1057, 1365, 1377, 1464, 2870, 2925, 2954, 3330 cm^{-1}.

1-*O*-Benzyl-2,3-bis-*O*-[(3*R*,7*R*,11*R*)-3,7,11,15-tetramethylhexadecan-1-yl]-*sn*-glycerol (34). Methanesulfonyl chloride (0.72 mL, 9.26 mmol) was added to a mixture of phytanol (**32**) (2.12 g, 7.12 mmol) in pyridine (10 mL) at 0 °C, and the solution was stirred at 0 °C for 2 h. Water (10 mL) was added, and the mixture was extracted with EtOAc. The organic phase was successively washed with 2 N HCl, saturated $NaHCO_3$, and brine, dried (Na_2SO_4), filtered, and concentrated to dryness to give crude mesylate **33** as an oil. This methanesulfonate was used for the next step without further purification. To a suspension of prewashed NaH (252 mg, 10.5 mmol) in DMSO (3 mL) was added a solution of 1-*O*-benzyl-*sn*-glycerol (**26**) (580 mg, 3.18 mmol) in DMSO (3 mL). After 1 h, a solution of the mesylate (2.46 g, 6.52 mmol) in DMSO (7 mL) was added. The mixture was stirred for 67 h at 40 °C. Saturated aqueous NH_4Cl (15 mL) was added, and the mixture was extracted with EtOAc. The organic phase was washed with water, dried (Na_2SO_4), filtered, and concentrated to dryness. The residue was chromatographed over silica gel with hexane−EtOAc (50:1) to give **34** (1.49 g, 63%) as an oil. $[\alpha]^{28}_D$: +2.85° (*c* 0.64, $CHCl_3$). ^{1}H NMR (300 MHz) δ: 0.83−0.88 (10 × d, 30H), 1.00−1.68 (m, 48H), 3.41−3.67 (m, 9H), 4.56 (s, 2H), 7.26−7.34 (m, 5H). ^{13}C NMR (67.5 MHz) δ: 19.75, 22.63, 22.72, 24.37, 24.48, 24.78, 27.96, 29.80, 29.89, 32.80, 36.62, 37.09, 37.27, 37.40, 37.45, 37.50, 39.36, 68.86, 69.94, 70.30, 70.78, 73.33, 77.93, 127.48, 127.57, 128.28, 138.42. IR (neat): 1115, 1380, 1376, 1460, 2860, 2920, 2950 cm^{-1}. Anal. Calcd for $C_{50}H_{94}O_3$: C, 80.79; H, 12.75. Found: C, 80.59; H, 12.82.

2,3-Di-*O*-[(3*R*,7*R*,11*R*)-3,7,11,15-tetramethylhexadecanyl]-*sn*-glycerol (1). A mixture of **34** (2.03 g, 2.74 mmol) and 10% Pd−C (1.11 g) in EtOAc (20 mL) was stirred for 29 h at 40 °C under hydrogen atmosphere. The catalyst was filtered through a pad of Celite and washed with EtOAc. The filtrate and washings were combined and concentrated to dryness. The residue was purified by flash chromatography over silica gel with hexane−EtOAc (20:1) to give **1** (1.63 g, 92%) as an oil. $[\alpha]^{25}_D$: +8.66° (*c* 1.07, $CHCl_3$). ^{1}H NMR (300 MHz) δ: 0.83−0.89 (m, 30H) 1.00−1.69 (m, 48H), 2.21 (t, J = 6.0, 1H), 3.44−3.76 (m, 9H). ^{13}C NMR (75 MHz) δ: 19.66, 19.69, 19.76, 22.62, 22.72, 24.34, 24.46, 24.79, 27.96, 29.83, 29.86, 32.78, 36.57, 37.05, 37.27, 37.34, 37.38, 37.44, 37.48, 39.36, 63.08, 68.63, 70.14, 70.94, 78.28. IR (neat): 1051, 1117, 1365, 1376, 1464, 2868, 2925, 2952, 3471 cm^{-1}. Anal. Calcd for $C_{43}H_{88}O_3$: C, 79.07; H, 13.58. Found: C, 78.91; H, 13.57.

(2*R*,7*R*,11*R*,15*S*,19*S*,22*S*,26*S*,30*R*,34*R*)-7,11,15,19,22,26,30,34-Octamethyl-2-[[[(*N*,*N*,*N*-trimethylamino)ethyl]phosphonyl]methyl]-1,4-dioxacyclohexatriacontane (35). To a solution of **2** (113 mg, 0.173 mmol) in pyridine (1 mL) was added (*β*-chloroethyl)phosphonyl dichloride (40 μL, 0.31 mmol) at 0 °C. The mixture was stirred for 2.5 h at room temperature. Water (5 mL) was added, and the mixture was stirred at room temperature for 1 h. Then, the mixture was acidified by addition of 2 N HCl and extracted four times with $CHCl_3$. The combined organic layer was dried (Na_2SO_4), filtered, and concentrated to dryness. The obtained residue was chromato-

graphed over silica gel with $CHCl_3$−MeOH (20:1−7:1) to give a waxy residue (172 mg). The residue was dissolved in toluene (10 mL) and CH_3CN (5 mL), and the solution was transferred into a pressure bottle. The mixture was cooled to −78 °C, and dry trimethylamine (10 mL) was introduced. The mixture was heated at 50−60 °C for 3 days. After removal of the solvent, the residue was chromatographed over silica gel with $CHCl_3$−methanol (8:1) to $CHCl_3$−methanol−H_2O (65:15:1) to give **35** (85 mg, 60%) as a hygroscopic wax. ^{1}H NMR (300 MHz, $CDCl_3$:CD_3OD = 8:1) δ: 0.85−0.90 (m, 24H), 1.00−1.50 (m, 44H), 1.53−1.67 (m, 8H), 3.23 (s, 9H), 3.45−3.56 (m, 3H), 3.58−3.66 (m, 6H), 3.88 (t, J = 5.6, 2H), 4.26 (br, 2H). ^{13}C NMR (75 MHz, $CDCl_3$:CD_3OD = 4:1) δ: 19.29, 19.34, 19.44, 19.47, 19.53, 19.57, 19.63, 19.67, 19.81, 23.58, 23.63, 23.77, 23.82, 23.95, 24.00, 24.14, 29.36, 29.40, 29.44, 29.60, 31.85, 31.87, 32.07, 32.09, 32.15, 32.30, 32.34, 32.38, 32.50, 32.69, 32.96, 32.98, 33.70, 33.73, 36.20, 36.25, 36.39, 36.46, 36.49, 36.56, 36.63, 36.74, 36.76, 36.80, 36.89, 36.94, 36.98, 37.01, 37.07, 37.13, 37.18, 53.92, 58.70 (d, J = 4.4), 64.86 (d, J = 5.6), 66.18, 66.23, 66.26, 68.41, 69.72, 70.54, 77.67 (d, J = 8.6). High-resolution FAB-MS: calcd for $C_{48}H_{99}O_6NP$ (M^+ + H) 816.7210, found 816.7210.

2,3-Bis-*O*-[(3*R*,7*R*,11*R*)-3,7,11,15-tetramethylhexadecan-1-yl]-*sn*-glycero-1-phosphocholine (36). By the same manner as described in the synthesis of **35**, the compound **1** (206 mg, 0.315 mmol) was converted to **36** (109 mg, 44%) as a hygroscopic wax. ^{1}H NMR (400 MHz) δ: 0.83−0.88 (m, 30H), 1.00−1.41 (m, 40H), 1.46−1.64 (m, 8H), 3.24 (s, 9H), 3.45−3.50 (m, 3H), 3.54−3.66 (m, 6H), 3.88 (t, J = 6.0, 2H), 4.25 (br, 2H). ^{13}C NMR (100 MHz, $CDCl_3$−CD_3OD = 8:1) δ: 19.39, 19.47, 22.36, 22.45, 24.15, 24.24, 24.55, 27.71, 29.60, 29.71, 32.54, 32.71, 36.44, 36.88, 37.04, 37.19, 37.32, 39.13, 53.98, 58.71 (d, J = 3.6), 64.81 (d, J = 5.4), 66.14, 68.61, 69.87, 70.49, 77.77 (d, J = 7.3). High-resolution FAB-MS: calcd for $C_{48}H_{101}O_6NP$ (M^+ + H) 818.7367, found 818.7385.

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Supporting Information Available: ^{1}H and ^{13}C NMR spectra for compounds **1**, **2**, **5**−**14ab**, **17**−**24**, **27**−**30**, **32**, and **34**−**36**, ^{1}H NMR spectra of MTPA esters of **9** and **14b**, and mass spectra for compounds **2**, **30**, and **35** (56 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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